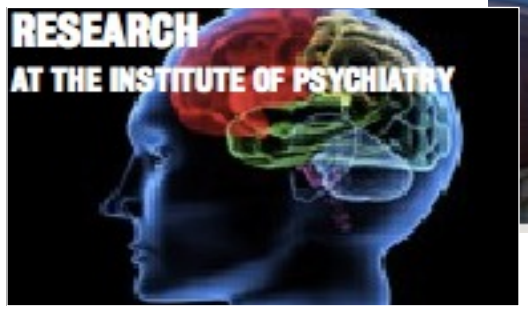

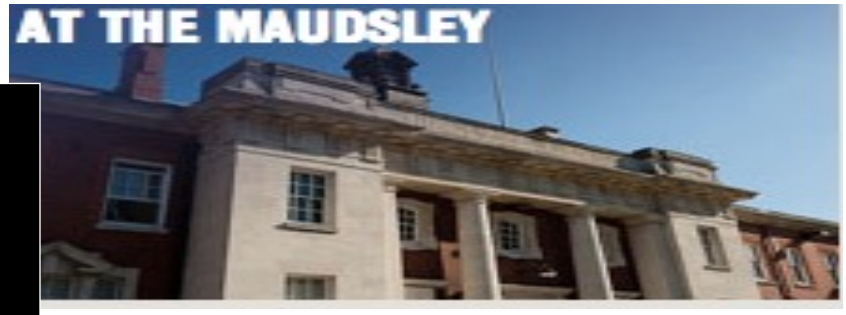

Treatment Resistance in Psychosis –
is clozapine the only game in town?

Professor Fiona Gaughran, Lead Consultant, National Psychosis Service

Director of R&D, South London and Maudsley NHS Foundation Trust

Professor of Physical Health and Clinical Therapeutics in Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London

https://slam.nhs.uk/national-services/adult-services/psychosis-service/

Declaration of Interests

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FG has received honoraria for lectures from Lundbeck, Otsuka, and Sunovion.

Remission and Recovery in first episode psychosis (FEP)

- Meta-analysis of 79 studies (19,072 FEP patients).
  - Pooled remission: 58% (60 studies, mean 5.5 y follow-up)
    - Higher remission rates in more recent years.
  - Pooled prevalence recovery: 38% (35 studies, av 7.2 y).
- GAP study 5-year follow-up of 246 people with FEP:
  - 81/240 (34%) “Treatment Resistant”
  - Of these, 70% had <u>never</u> remitted (23% of total):
- Why?
  - Different underlying biology?
  - Perpetuating factors? Co-morbidities?
  - Adherence? - Levels, LAIs?

Lally J, Ajnakina O, Stubbs B, Cullinane M, Murphy KC, Gaughran F, Murray RM. Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies. Br J Psychiatry. 2017 Dec;211(6):350-358. doi: 10.1192/bjp.bp.117.201475. Epub 2017 Oct 5. PMID: 28982659.

Psychological Medicine, doi:10.1017/S00332917

Assessment of Treatment Resistance

Diagnosis

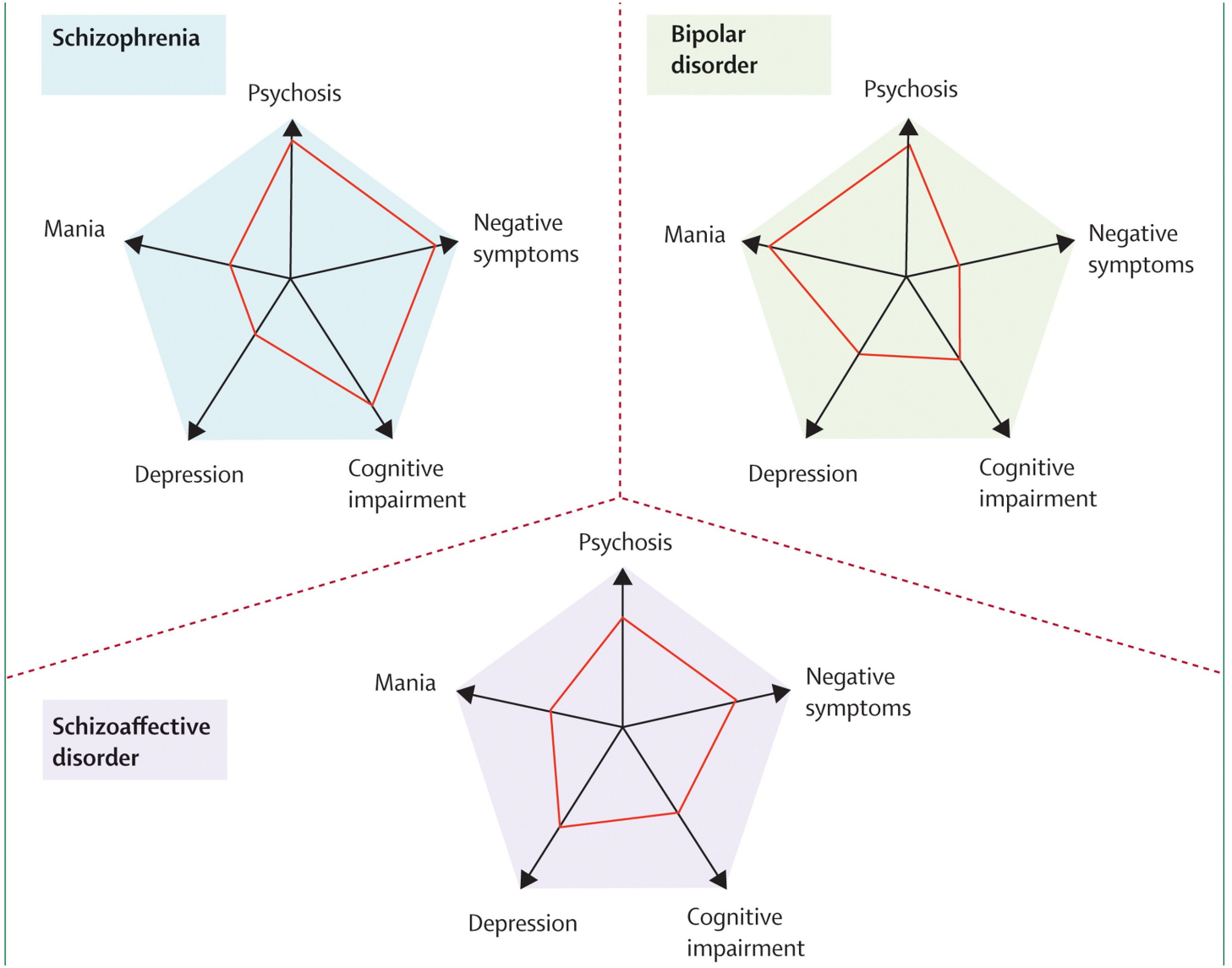
Dimensions

Co-morbidities

Physical health | Mental Health

What's been tried

Why didn't it work?

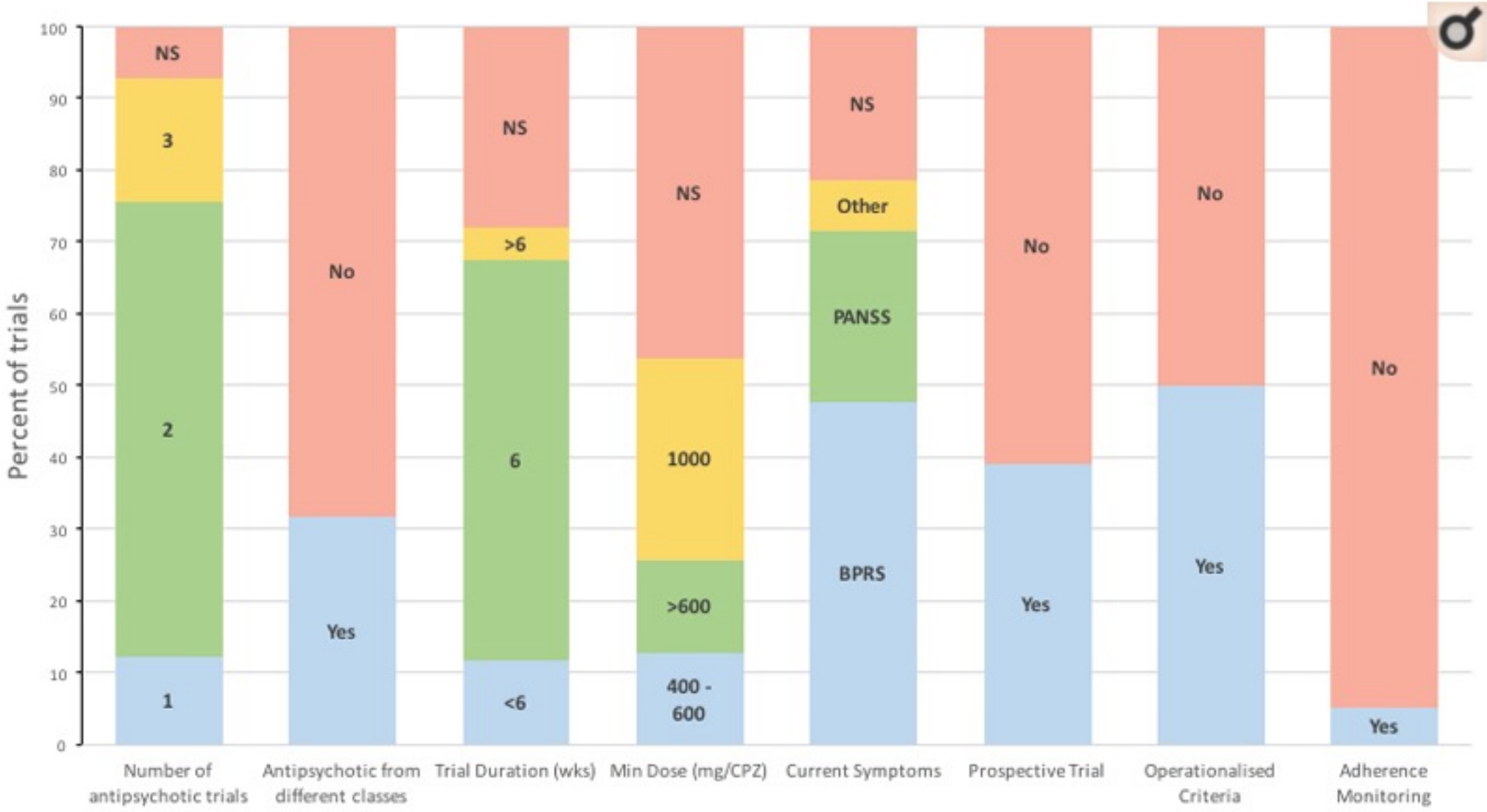


Van Os and Kapur, 2010

What is “Treatment Resistant Schizophrenia”?

All psychosis is not schizophrenia

Research definitions vary



Summary of criteria used in clinical trials of treatment resistant schizophrenia

NS – Not specified, CPZ – Chlorpromazine equivalents

Howes et al, 2017

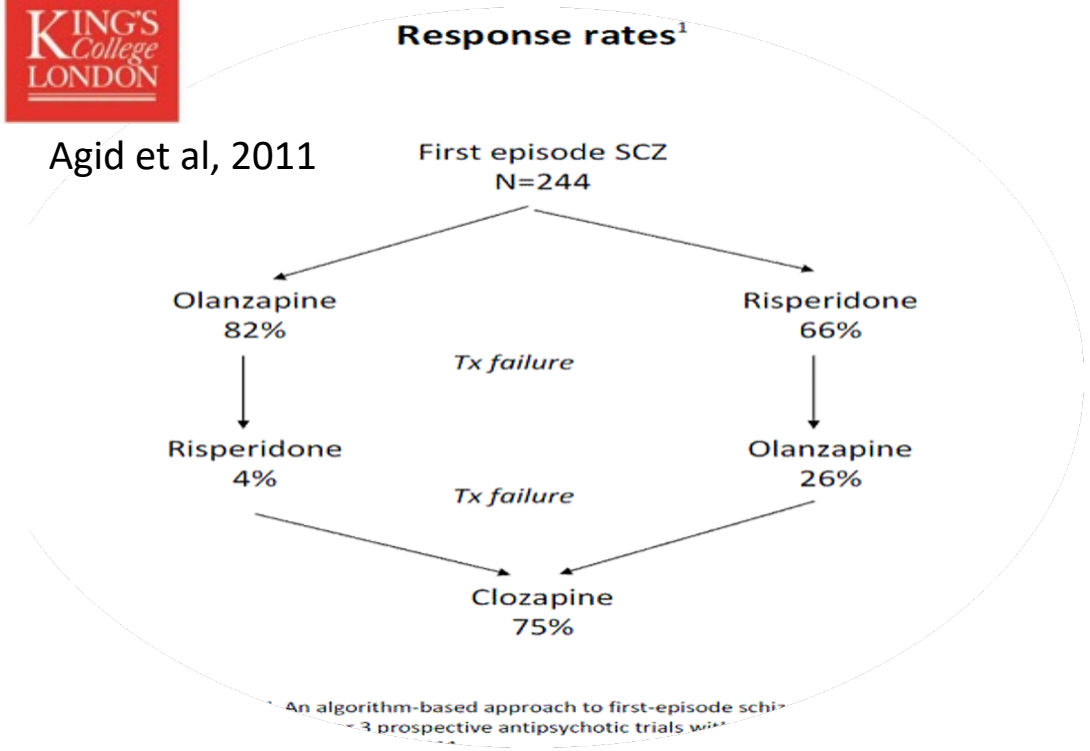
Consensus criteria for assessment and definition of treatment resistant schizophrenia

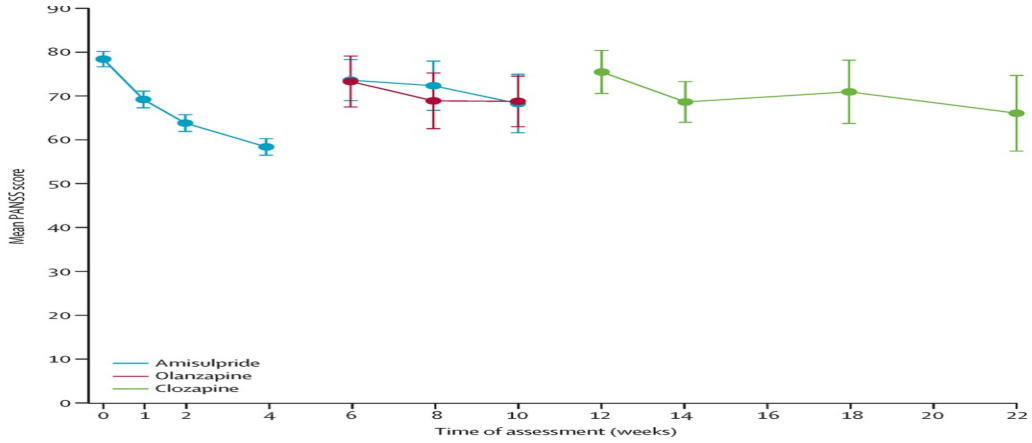
Domain	Subdomain	Minimum Requirement	Optimum Requirement
Current symptoms	Assessment	Interview using standardised rating scale (e.g., PANSS, BPRS, SANS, SAPS)	Prospective evaluation of treatment using standardised rating scale
	Severity	At least moderate severity	At least moderate severity and <20% symptom reduction during prospective trial/observation ≥6 weeks
	Duration	≥12 weeks	≥12 weeks. Specify duration of treatment resistance.
	Subjective distress	Not required	Not required
	Functioning	At least moderate functional impairment measured using a validated scale (eg z)	At least moderate functional impairment measured using a validated scale (eg SOFAS)
Adequate treatment	Assessment of past response	Information to be gathered from patient/carer reports, staff and case notes, pill counts and dispensing charts.	Information to be gathered from patient/carer reports, staff and case notes, pill counts and dispensing charts.
	Duration	≥6 weeks at a therapeutic dose Record minimum and mean (sd) duration for each treatment episode	≥6 weeks at a therapeutic dose Record minimum and mean (sd) duration for each treatment episode
	Dose	Equivalent to ≥600mg chlorporamzine per day[1] Record minimum and mean (sd) dose for each drug	Equivalent to ≥600mg chlorporamzine per day[1] Record minimum and mean (sd) dose for each drug
	Number of anti-psychotics	≥2 past adequate treatment episodes with different antipsychotic drugs Specify median number of failed antipsychotic trials.	≥2 past treatment episodes with different antipsychotic drugs and at least one utilizing a long-acting injectable antipsychotic (for at least 4 months). Specify median number of failed antipsychotic trials.
	Current Adherence	≥80% of prescribed doses taken. Adherence should be assessed using ≥ 2 of pill counts, dispensing chart reviews and patient/carer report. Antipsychotic plasma levels monitored on at least one occasion. Specify methods used to establish adherence.	As for minimum criteria and additionally trough antipsychotic serum levels measured on at least two occasions separated by at least two weeks (without prior notification of patient).
Symptom Domain		Positive/Negative/Cognitive	
Time course		Early-onset (within 1 year of treatment onset)/ Medium-term onset (within >1-5 years of treatment onset)/ Late-onset (after >5 years of treatment onset)	
Ultra-treatment resistant: clozapine		Meets the criteria for treatment resistance above plus failure to respond to adequate clozapine treatment[2]	

BPRS- Brief Psychiatric Rating Scale; CGI-S-TRS - Clinical Global Impressions-Severity Treatment Resistant Schizophrenia scale; PANSS- Positive and Negative Syndrome Scale; ECT - Electro-convulsive therapy; SANS - Scale for the Assessment of Negative Symptoms; SAPS - Scale for the Assessment of Positive Symptoms; SOFAS- Social and Occupational Functioning Scale

Howes et al, 2017

Agid et al, 2011





OPTIMISE (Kahn et al, 2018) Positive and Negative Syndrome Scale (PANSS) scores per visit for phases 1, 2, & 3 (mean and 95% Cis).

For resistant schizophrenia, clozapine has the best chance of working

- Sooner is better: Delay in starting clozapine linked to poorer outcomes.
- A mean of up to four years from eligibility to starting - too long!
- Regional variations
- Cost effective
- More independent living; fewer sections and hospitalisations
- Reduced mortality gap (suicide)

Shah, Remington et al, 2018; Howes et al, 2012: Davies et al, 2008; Tiihonen et al, 2016, Cho et al, 2018: Wheeler et al 2008

Before starting clozapine:

1. Reassess the diagnosis:
    1. Is it schizophrenia?
    2. Is there an undermanaged affective disorder? – bipolar disorder, psychotic depression, schizoaffective disorder or affective co-morbidity with schizophrenia
    3. Other modifiable co-morbidities? eg anxiety disorders
    4. Consider organic contributors, substance use and social factors
2. Is the psychosis treatment resistant?
    1. Are they taking the agreed treatment? Have you access to therapeutic blood levels? Would the patient prefer a Long Acting Injection?
    2. Is tolerance limiting treatment options – ALWAYS address side effects.

If you're going to do it, do it right: Optimising Clozapine

Levels are very useful but <u>treat the patient, not the levels</u>

Women, elderly, Asian and non-smokers achieve higher levels at a given dose

Adjust dose with change in smoking habits

Target levels 0.35-0.6mg/L

Some people may need higher levels, with seizure prophylaxis and caution about tolerance.

Some respond to lower levels, though we can't diagnose non-response below this level.

Ng et al, 2005; de Leon, Kane et al, 2020

Ask about Clozapine side effects and manage pro-actively

Side effect scale eg, **GASS-C** (Hynes et al, 2015) or **GASS plus Bristol Stool chart**

Maudsley Prescribing Guidelines

Maudsley Practice Guidelines for Physical health in Psychiatry

Gaughran TRS 2021

Haematological	Neutropaenia, agranulocytosis
Cardiac	Myocarditis(CRP/ Troponin) Cardiomyopathy, Pericarditis, Benign tachycardia
Cardiometabolic	Weight gain, Diabetes, lipids
Constipation	
Reduced seizure threshold at higher doses	
Hypersalivation	
Eneuresis	
Sedation	
Respiratory	Pneumonia

Management of clozapine treatment during the COVID-19 pandemic

Siobhan Gee, Fiona Gaughran, James MacCabe, Sukhi Shergill, Eromona Whiskey and David Taylor

Ther Adv Psychopharmacol
2020, Vol. 10: 1–10
DOI: 10.1177/2045125320928167

- Clozapine levels increase with infection & on stopping smoking (CYP 1A2)
- Existing increased risk of pneumonia
- Lower immunoglobulins (Ponsford et al, 2019)
- WCC (total, Neutrophil, Lymphocyte) drops in covid-19 infection (Gee & Taylor, 2021)
- Social distancing: Maximise intervals between blood tests (and for depots, where applicable)
- Vaccination strategies; influenza, pneumococcus, Covid (group 6)

<u>Clozapine initiation: dilemmas</u>

- Initiation associated with hypotension, tachycardia, fever, sedation
- Peak risk period for
  - Myocarditis (fever, flu-like, fatigue, dyspnoea).
  - Sepsis
- Possible overlap with symptoms of Covid-19.
- Regular blood / vital signs
- Antigen tests where indicated
- Infection Prevention and Control pathways

https://www.rcpsych.ac.uk/about-us/responding-to-covid-19/responding-to-covid-19-guidance-for-clinicians/community-and-inpatient-services/providing-medication

Gaughran TRS 2021

Rechallenge with clozapine post Adverse Event?

Risk versus benefit, weighed against alternative strategies

If clozapine's not working well enough:

What next?

Management of clozapine non-response

- Optimise clozapine, checking levels
- Manage adverse effects proactively
- Reassess diagnosis
- Actively manage comorbidities eg, OCD; depression (bipolar or unipolar); hypomania/ mania; substance use
- Consider trial of supratherapeutic clozapine levels (i.e.>0.5 mg/l), with seizure prophylaxis. Reduce if ineffective
- Psychological therapies: CBTp, family work
- And then…

Lally & Gaughran 2019; Lally et al, 2016

Is it worth augmenting clozapine?

And if so, with what?

Clozapine Augmentation

Umbrella review of 21 meta-analyses of clozapine combination or augmentation strategies

- No strategies met Scottish SIGN Grade A criteria
- Augmentation meeting lower quality Grade B:
  - Second-generation and first-generation antipsychotics
  - ECT for clozapine-resistant positive symptoms
  - certain antidepressants (fluoxetine, duloxetine, citalopram) for persistent negative symptoms.
- Augmentation meeting Grades C–D only:
  - mood-stabilisers, anticonvulsants, glutamatergics (eg glycine, memantine), repetitive TMS, tDCS or CBT.

Wagner, Lohrs, Siskind et al, 2019:

Augmenting clozapine with an anti-psychotic

- Often disappointing in practice
  - If excess dopamine isn't the problem, dopamine antagonists may not be the solution
- High dose guidelines
  - Withdraw if no effect after 3-6 months
- Most common:
  - amisulpride (may allow clozapine dose reduction),
  - risperidone (1 positive, 2 negative RCTs)
- Augmenting for tolerance:
  - aripiprazole 5-15mg - -
    - Reduction in metabolic risk
    - lower clozapine doses needed

Maudsley Prescribing Guidelines, Taylor et al, 13th Edition; Smith et al, 2014; Fleischhacker W et al, 2010; Earley et al, 2019; Loebel et al, 2014

Alternatives to Clozapine

- Many RCTs / case reports
  - 4-page table in Maudsley Prescribing Guidelines, but no clear winner.
- Choice guided by diagnosis, dimensions of illness, co-morbidities, tolerance and adherence
- High Dose Olanzapine (not an 'atypical' dose) – no advantage over clozapine
  - Equivalent effect on psychopathology; Clozapine better on GAF but weight gain worse on Olanzapine
- Combinations
  - Common (POMH UK 43%) but evidence is limited and risk benefit unclear
  - Cochrane: Limited superiority to monotherapy in improving response (RR 0.73, 95% CI 0.63 to 0.85); NB positive results due to combination with clozapine (as in Scandinavian big data, Tiihonen 2019)
  - Correll et al, MA, 2017:
    - Effect size of co-prescribing strategies inversely correlates with trial quality.
    - No single strategy can be recommended

Maudsley Prescribing Guidelines, 13th edition , Taylor et al;

Correll et al, JAMA Psychiatry. 2017; Galling B, et al. World Psychiatry. 2017 Feb;16(1):77-89: Meltzer er al, 2008

Address mood <u>if</u> <u>evidence of mood disturbance</u>

- Lithium Meta-analysis (22 studies, n=763) of lithium + anti-psychotic in schizophrenia/schizoaffective
  - Augmentation shows an effect…but this vanished when schizoaffective disorder was excluded!
- Valproate
  - Evidence limited: No effect if open trials excluded
  - Less aggression but more sedation
  - NB - **Teratogenic – see recent BAP guidance**
- Evidence in schizoaffective disorder largely not tailored to current mood states
- BAP – consider mood stabiliser in schizoaffective if manic symptoms persist after adequate trial of anti-psychotic
- Anti-depressants produce response in major depressive disorder in schizophrenia NNT= 5 (95% CI 4-9), though no difference in follow-up depression scores
- Review of data from 4 trials: lurasidone improved depressive symptoms in schizophrenia

Leucht et al, 2015, 2016, Gregory, Upthegrove et al, 2017 Nazrallah et al, 2014, Barnes et al

Negative and Cognitive Symptoms

Flattened affect, alogia, anhedonia, social withdrawal, avolition and lethargy.

Negative Symptoms:

- Huge impact on function, but relatively neglected.
    - Not systematically recorded
    - No consensus on screening for secondary negative symptoms
- MA 2015, 2017: SGAs (including clozapine) have statistical but not clinically significant effect.
- Combination strategies not effective (Correll 2017)
- Recent drugs in development, eg Glycine transporter 1 inhibitor, did not reach primary outcome
- Post hoc industry analysis suggests effect for cariprazine; needs replication

Cognition:

- Review of cognitive enhancers: small effect. Most act on glutamatergic and cholinergic systems
- Best strategy is to give lowest effective dose of anti-psychotics (BAP)

Fleischhacker et al, 2019; Sinkeviciute et al, 2018, Fusar-Poli, 2015, Leucht et al, 2017, Correll et al, 2017, Barnes et al, 2019

Psychological & psychosocial interventions

- CBT most recommended
  - Cochrane Review: no clear advantage over other psychosocial therapies in schizophrenia (Jones et al, 2018)
- Family Work
- Art Therapies – Matisse negative
- Cognitive Remediation
- Under development/evaluation
  - Trauma focussed approaches
  - Avatar therapy
- Occupational Therapy
  - daily function, activities, re-training, social engagement
- Diet
- Smoking Cessation
- Exercise
  - Benefits physical health, cognition, mood, hippocampal size
- Physiotherapy
  - Pain/ falls /fractures

So, once clozapine is indicated in schizophrenia, there is no single simple alternative

Anything on the horizon?

Anti-inflammatory drugs in Resistant Psychosis

Minocycline – early promising studies; recent larger Benemin trial showed no effect on negative or other symptoms of schizophrenia.

Minocycline in adolescence (for acne) does not reduce the risk of severe mental illness in adulthood (Herrero-Zazo et al, 2018)

Aspirin (1000mg) reduced psychotic symptoms, especially in those with high CRP (Laan et al, 2010)

Adjunctive N-acetyl cysteine (Zheng et al, 2018) safe with some efficacy for schizophrenia (also glutamatergic effect)

MA - aspirin, oestrogens, minocycline, and NAC: better in early psychosis (Sommer et al, 2019)

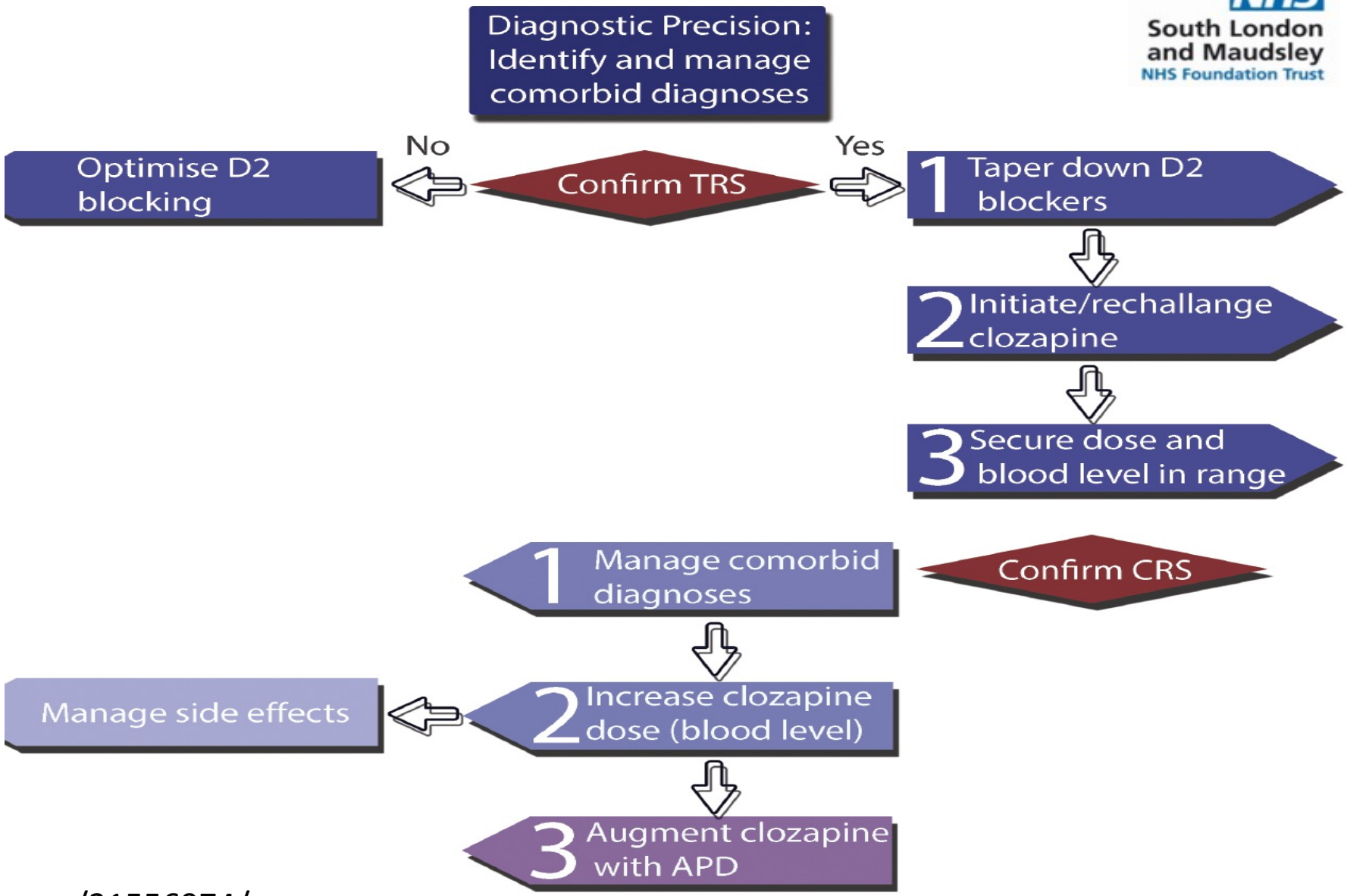
BAP guidance (Barnes et al) The evidence is insufficient to recommend the use of anti-inflammatory medications for schizophrenia in clinical practice.

Hormonal Approaches to resistant psychosis

- **Oestradiol** (an anti-inflammatory) –in pre-and post-menopausal women (Kulkarni et al, 2015, 2016).
  - Not unopposed with intact uterus (risk of cancer).
  - IUD with progesterone may allow use.
  - Systemic progesterone has independent effect, not trialled
- **Selective Oestrogen Receptor Modulators** – eg Raloxifene
- Affects brain and bone but not breast and uterus.
- Recent MA; effect on total, positive, negative and general PANSS scores, with similar adverse events and discontinuation rates (Zhu XM et al, 2018)

- Good practice: Routinely screen for menopausal symptoms

Treatment resistant schizophrenia algorithm



https://pubmed.ncbi.nlm.nih.gov/31556974/

Real-world outcomes in the management of refractory Psychosis; Krivoy et al, 2019

Is clozapine the only game in town?

For true treatment resistant schizophrenia, clozapine gives best chance of success and should be started early

- **Optimise & manage side effects**
- **Augment clozapine in partial responders**
- **Limited data for alternatives;**
  - **high olanzapine, combinations, ECT**

Evidence more limited for schizoaffective disorder

- **Clozapine helpful, but important to address mood**

For all psychoses, combine with psychosocial interventions

Manage physical health needs, including covid-19

Questions?

Prevalence and Predictors of Clozapine-Associated Constipation: A Systematic Review and Meta-Analysis

Ayala Shirazi [1], Brendon Stubbs [2,3], Lucia Gomez [1], Susan Moore [4], Fiona Gaughran [4,5], Robert J. Flanagan [6], James H. MacCabe [4,5] and John Lally [4,5,*]

Constipation in schizophrenia:

- Sedentary lifestyle, obesity, low fiber intake, dehydration.

Clozapine reduces GI motility;

- muscarinic anti-cholinergic activity;
- Norclozapine; opioid receptor agonism

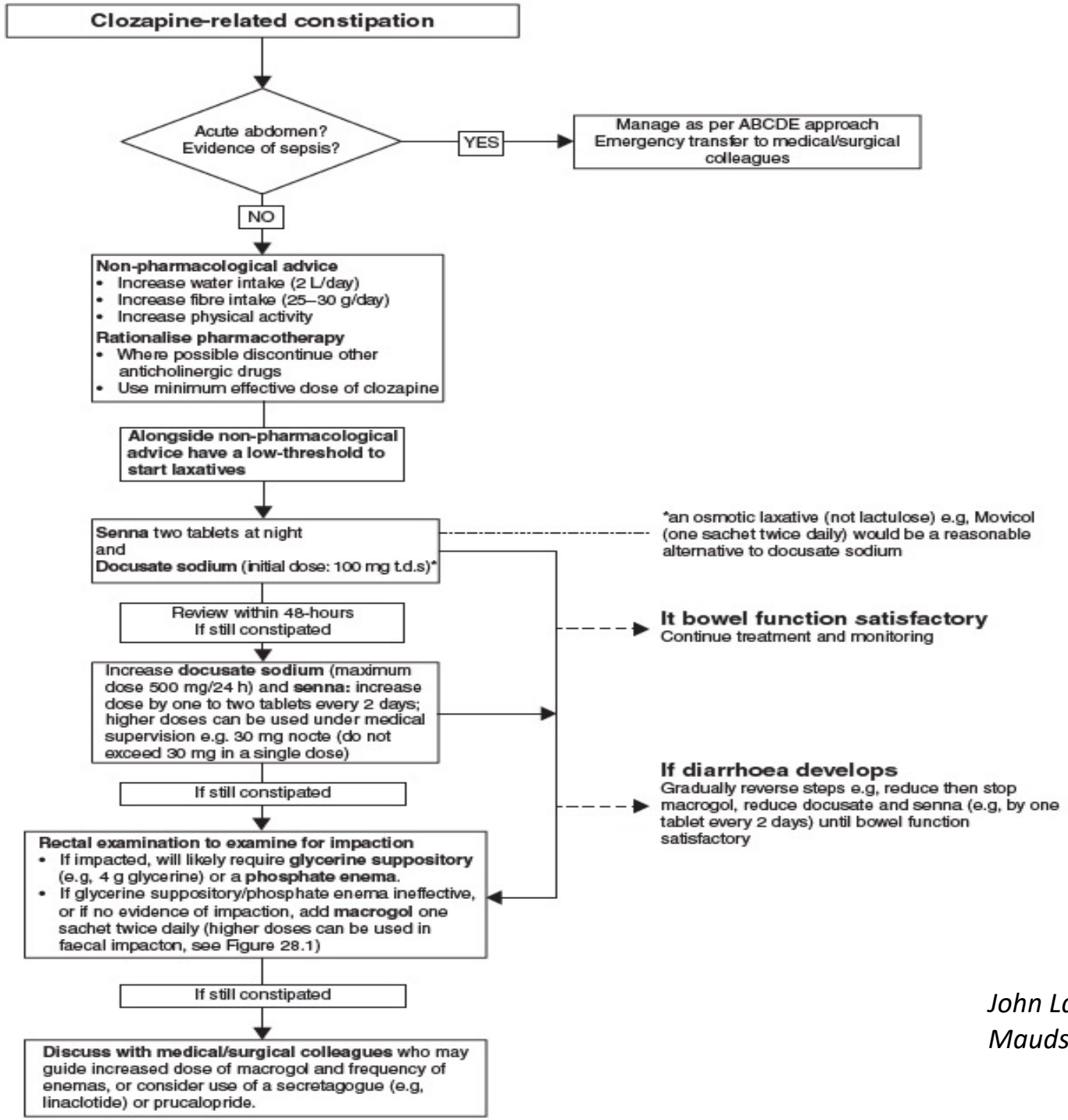
Prevalence of clozapine-associated constipation: 31.2%

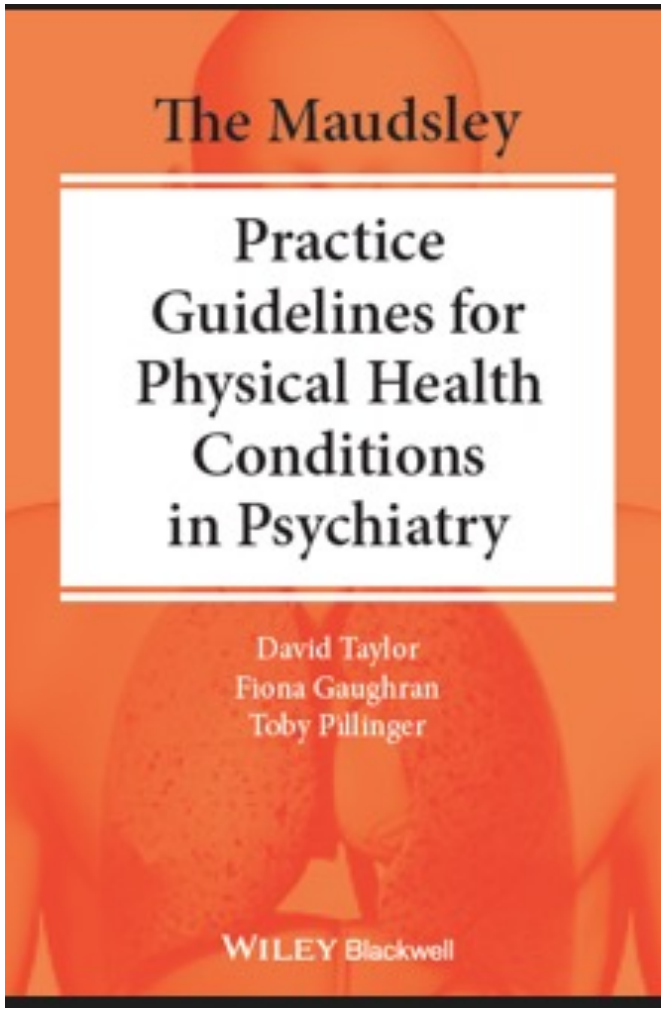
3 times as likely as on other antipsychotics

Not dose/level related

Danish data: 0.8% ileus

Int. J. Mol. Sci. 2016, 17, 863; doi:10.3390/ijms17060863





John Lally, Toby Pillinger, Kalliopi Vallianatou, Immo Weichert
Maudsley Practice Guideline for Physical Health, 2020